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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,511	10/24/2005	Hermona Soreq	74136/JPW/JW	2199

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/529,511	SOREQ ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The application filed on October 24, 2005 has been received and entered. Claims 2-4 are pending. Accordingly, claims 2-4 are examined on the merits herewith.

Specification

The disclosure is objected to because of the following informalities. Pages 12 and 19 recite the mutation H332N in the AChE gene, while the rest of the specification (see for example, pp. 16 and 27) recites the mutation H322N. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the term "PD susceptibility haplotype." The meaning of this term is unclear and undefined, as a number of genetic mutations are associated with PD (see below and see Applicants' IDS filed on March 20, 2006), rendering the meaning of the claims unclear. Pages 19 and 27 disclose that Applicants' PD susceptibility haplotype is PON1 L55M, Q192R/AChE del HNF3, H322N, P446. Appropriate correction is required. It is suggested that the claims be amended to recite this definite haplotype, i.e., a method of predicting susceptibility to Parkinson's Disease (PD), or a method of screening for a genetic predisposition to Parkinson's Disease (PD), comprising detecting the presence of the haplotype PON1 L55M, Q192R/AChE del HNF3, H322N, P446 in the DNA from a blood sample from an individual.

Applicants should note, for prior art purposes and with respect to 35 USC § 112, that the claims are interpreted as reciting PON1 L55M, Q192R/AChE del HNF3, H322N, P446 as the PD susceptibility haplotype.

Additionally, the claims recite the term "PD," rendering the meaning of the claims unclear. Independent claims may not recite an abbreviation, as the full name of the abbreviated term must appear. The term "PD" should be amended to "Parkinson's disease" or Parkinson's disease (PD)." An abbreviation such as PD may be used in dependent claims if the claims from which they depend recite the full name of the disease.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 2 recites a method, but does not recite any steps. The omitted steps are: obtaining a blood or tissue sample from an individual, isolating the DNA from the cells in the sample and determining the presence of the haplotype PON1 L55M, Q192R/AChE del HNF3, H322N, P446 in the DNA in this sample.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure- the recitation in the claims- which is not enabling. The claims recite a method for predicting the likelihood of developing Parkinson's disease- i.e., the susceptibility or the predisposition of a subject for developing Parkinson's disease (PD). The claimed method is based solely on determining the presence of the "PD-susceptibility haplotype" in a subject's DNA. This

haplotype is a pair of groups of mutations totaling five mutations: the PON1 mutations L55M and Q192R and the AChE mutations del HNF3, H322N and p446. Applicants' data, however, do not demonstrate that an individual is more likely to develop PD only because he or she has these genetic mutations. But, Applicants' data do show that an individual that has these five mutations and that has been exposed to substantial dosages of an organophosphate compound, in particular an agricultural insecticide, has an elevated risk of developing PD. See Example 4, pp. 40-41. The data in Example 3, p. 39, show that in comparing normal subjects and Parkinson's patients, the frequencies of the PON1 alleles 55L, 55M, 192Q and 192R do not vary greatly. Larger differences are present between Japanese and European people than between normal and Parkinson's subjects. This disclosure is critical or essential to the practice of the invention, but it is not included in the claim(s) or enabled by their disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Thus, the claims fail to satisfy the enablement requirement. Applicants may wish to amend the claims to recite a method for predicting the susceptibility of an individual for developing PD, or a method of determining the genetic predisposition of individual for developing PD, comprising determining the presence of the alleles PON1 L55M, Q192R and AChE del HNF3, H322N, P446 and determining that the individual has been exposed to an organophosphate insecticide or neurotoxin.

Art of Record

The following references, although submitted in Applicants' Information Disclosure Statement on March 20, 2006, are discussed below to disclose further the state of the art at the time that the invention was filed.

Kondo et al. ("Genetic polymorphism of paraoxonase 1 (PON1) and susceptibility to Parkinson's disease," Brain Res 806:271-273, 1998, disclose that, with respect to PON1

enzymatic activity, individuals fall into three groups, AA (high activity) AB (medium activity) and BB (low activity). The lower the PON1 activity is, the greater the likelihood is that an individual will develop PD or suffer toxic effects from an organophosphate pesticide or neurotoxin. AA represents Q/Q, AB represents Q/R and BB represents R/R for the amino acid at position 192 of PON1 (see pp. 271-272). Thus, Kondo et al. disclose that susceptibility to PD may be determined by measuring an individual's PON1 activity or by identifying his alleles at this one genetic locus.

Akhmedova et al. ("Paraoxonase 1 Met-Leu 54 polymorphism is associated with Parkinson's disease," J Neurol Sci 184:179-182, 2001) disclose that the L55M mutation is associated with early-onset PD and that the presence of the M allele, either homozygously or heterozygously (MM or LM genotype) increases the likelihood of developing early-onset PD (see p. 181). Thus, Akhmedova et al. disclose that susceptibility to PD may be determined by identifying an individual's alleles at this one genetic locus.

Kaufer et al. ("Tracking cholinergic pathways from psychological and chemical stressors to variable neurodeterioration paradigms," Current Opinion in Neurology 12:739-743, 1999) disclose that chronic exposure to organophosphate pesticides (acetylcholinesterase inhibitors) is a risk factor for developing PD and that up to one-third of Parkinson's patients suffer from cholinergic deficiencies. Kaufer et al. do not disclose a genetic basis for PD, but they disclose that the development of PD is associated with a defective acetylcholinesterase gene.

Shapira et al. ("A transcription-activating polymorphism in the AChE promoter associated with acute sensitivity to anti-acetylcholinesterases," Human Molecular Genetics 9(9):1273-1281, 2000) disclose that organophosphate insecticides and neurotoxins cause chemical hypersensitivity and overstimulate the production of acetylcholinesterase. These compounds are acetylcholinesterase inhibitors. Shapira et al. also disclose the double mutation del HNF3

and H322N in the acetylcholinesterase gene and that this mutated gene is associated with chemical hypersensitivity to organophosphate toxins and the overproduction of acetylcholinesterase (see pp. 1273-1275). Shapira et al. do not disclose that this double mutation is associated with PD, but they disclose that the acetylcholinesterase gene may be rendered defective because of mutations or because of exposure to organophosphate neurotoxins.

Based on the teachings of Kaufer et al. and Shapira et al., it would have been obvious to one of ordinary skill in the art at the time that the invention was made to investigate the linkage between genetic defects in the acetylcholinesterase gene and the development of PD.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2006-10-20

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER